Rejection of Claim 2 Under 35 U.S.C. §112, Second Paragraph

Claim 2 is rejected by the Examiner under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner has stated that Claim 2 is indefinite because the phrase "the nucleotide to be queried in the target polynucleotide sequence" lacks proper antecedent basis.

Applicants have amended Claim 2 to recite proper antecedent basis. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 2 under 35 U.S.C. §103(a)

Claim 2 is rejected by the Examiner under 35 U.S.C. §103(a) as being unpatentable over Ugozzoli *et al.* in view of the Stratagene Catalog (page 39 (1998); Ref. W). Essentially, the Examiner has maintained the rejection presented in the Office Action mailed from the United States Patent and Trademark Office on February 27, 2002 (paper no. 14, at page 3). However, it appears that this rejection has not accounted for Applicants' claim amendments as the Examiner has stated that "Claim 2 is drawn to a kit comprising two components" (Office Action, page 3, emphasis added). Applicants respectfully note that Claim 2, as amended, is drawn to a three component kit comprising (1) an array of one or more oligonucleotide tags fixed to a solid substrate and (2) one or more locus-specific tagged oligonucleotides, wherein each locus-specific tagged oligonucleotides has at its 5' end a sequence which hybridizes to the arbitrary sequence of a corresponding oligonucleotide tag on the array, and at its 3' end a nucleotide sequence complementary to the target polynucleotide sequence in a sample, wherein the last nucleotide at the 3' end of the locus-specific tagged oligonucleotide hybridizes exactly one nucleotide before the target nucleotide to be queried, and (3) at least two labeled dideoxynucleotides (ddNTPs). The teachings of Ugozzoli *et al.* are specific to the two-allele polymorphism of the human tyrosine gene. Ugozzoli *et al.* do not teach the use of labeled dideoxynucleotides, see, for example, page 109 under section heading AS-PE, wherein Ugozzoli *et al.* use labeled dGTP and TTP, not ddNTPs.

The Stratagene Catalog merely lists kits for general gene characterization. It does not teach or suggest the primers as recited in the instant claims in combination with a labeled dideoxynucleotide. Applicants do not concede that the cited references are properly combined. However, even in combination, Ugozzoli *et al.* and the Stratagene Catalog fail to teach or suggest all the claim limitations of the present invention, because even if the components taught by Ugozzoli, *et al.* were formulated into a kit, they would still fail to teach or suggest a kit comprising an array of oligonucleotide tags and the primers of the present invention in addition to at least two ddNTPs. Therefore, a *prima facie* case of obviousness has not been established.

Rejection of Claim 20 Under 35 U.S.C. §102(b)

Claim 20 is rejected by the Examiner under 35 U.S.C. §102(b) as being anticipated by Ugozzoli *et al.* (GATA 9(4): 107-112 (1992); Ref. U). Specifically, the Examiner states that "Ugozzoli et al. teach a set of primers comprising all the limitations of Claim 20 . . . ." (Office Action, page 4).

Applicants respectfully disagree. Claim 20 is drawn to kit comprising (a) a pair of primers which when in the presence of DNA polymerase amplify a region of double stranded DNA, wherein the region comprises a polymorphic locus, and (b) an extension primer which comprises 3' portion which is complementary to a portion of the region of double stranded DNA and a 5' oligonucleotide portion which is not complementary to the region of double stranded DNA, but which is complementary to a unique known sequence of an oligonucleotide tag fixed to a solid substrate, wherein the extension primer is complementary to the 3' nucleotide sequence of the polymorphic locus, and wherein the last nucleotide at the 3' end of the extension primer hybridizes exactly one nucleotide before the polymorphic locus and (c) at least two dideoxynucleotides, each of which are distinctly labeled.

Ugozzoli *et al.* do not teach a kit comprising the primers of the present invention with at least two distinctly labeled dideoxynucleotides. For example, Ugozzoli *et al.* only teach the use of labeled deoxyguanosine triphosphate (dGTP), but not dideoxyguanosine triphosphate (ddGTP), see, for example, page 109 under section heading AS-PE. Thus, Ugozzoli *et al.* fail to teach each and every aspect of the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 20 Under 35 U.S.C. §103(a)

Claim 20 is rejected by the Examiner, in the alternative to being rejected under 35 U.S.C. §102(b) (see above), under 35 U.S.C. §103(a) as being obvious over Ugozzoli *et al.* (Office Action, page 4).

Specifically, the Examiner alleges that "Ugozzoli et al. teach a set of primers comprising all of the limitations of Claim 20. . . ." However, as Applicants have already stated above, Ugozzoli *et al.* do not teach a kit comprising the primers of the present invention with at least two distinctly labeled dideoxynucleotides.

Claim 20 is drawn to kit comprising (a) a pair of primers which when in the presence of a DNA polymerase amplify a region of double stranded DNA, wherein the region comprises a polymorphic locus, and (b) an extension primer which comprises a 3' portion which is complementary to a portion of the region of double stranded DNA and a 5' oligonucleotide portion which is not complementary to the region of double stranded DNA, but which is complementary to a unique known sequence of an oligonucleotide tag fixed to a solid substrate, wherein the extension primer is complementary to the 3' nucleotide sequence of the polymorphic locus, and wherein the last nucleotide at the 3' end of the extension primer hybridizes exactly one nucleotide before the polymorphic locus and (c) at least two dideoxynucleotides, each of which are distinctly labeled.

Ugozzoli *et al.* do not teach or suggest each and every element of Claim 20. Ugozzoli *et al.* do not teach or suggest a method using dideoxynucleotides, nor do Ugozzoli *et al.* teach or suggest a kit comprising the primers of the present invention and at least two labeled dideoxynucleotides. Therefore the teachings of Ugozzoli *et al.* fail to establish a *prima facie* case of obviousness. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 21-24 Under 35 U.S.C. §103(a)

Claims 21-24 are rejected by the Examiner under 35 U.S.C. §103(a) as being "unpatentable over Ugozzoli et al. (1992) as applied against Claim 1 above and further in view of the Stratagene Catalog (1988) and Shumaker et al. (1996)."

Applicants note that the Examiner has referred to Claim 1 in this rejection. However, since Claim 1 is not under consideration in this application, Applicants anticipate that the

Examiner is referring to Claim 20, and the Examiner's intended rejection is as applied to Claim 20 under 35 U.S.C. §103(a) as being obvious over Ugozzoli *et al.* as discussed above.

Specifically, the Examiner has rejected Claim 21, alleging that "it would have been *prima facie* obvious to the ordinary artisan at the time of the invention to modify the teachings of Ugozzoli et al. in view [of the] Stratagene Catalog with the teachings of Shumaker et al. in order to arrive at the claimed invention. The ordinary artisan would have been motivated to make this modification in order to take advantage of the efficiency afforded by multiplexing and analyzing multiple different polymorphic loci in a single assay or at the least simultaneously in separate assays. In addition the ordinary artisan would have been motivated to make the modification recited above in order to eliminate the use of the dangerous radioactive reagents taught by Ugozzoli by using instead the fluorescently labeled ddNTPs of Shumaker et al." (Office Action, page 5).

According to MPEP §706.02(j), there are three basic criteria which must be met in order to establish a *prima facie* case of obviousness:

> First, there must be some suggestion or motivation in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations.

Ugozzoli *et al.* teach a method of detection for the two-allele polymorphism of the human tyrosinase gene (see Abstract). Ugozzoli *et al.* do not teach a kit comprising the primers of the present invention and at least two distinctly labeled dideoxynucleotides. Furthermore, Ugozzoli *et al.* do not teach a method using dideoxynucleotides.

The Stratagene Catalog, as noted earlier, only lists kits for general gene characterization. There is no teaching or suggestion of the primers claimed in the present invention, nor of their combination with dideoxynucleotides to make the claimed invention.

Shumaker *et al.* (Human Mutation 7 : 346-354 (1996); Ref. V) teach two distinct mutation detection methods (see, for example, Abstract). The first mutation detection method (the "Gel-based Assay," for example, at p. 347, second column) anneals extension primers to

DNA that is bound to a magnetic bead. The extension primers used in the gel-based assay of Shumaker *et al.* do not provide a teaching or suggestion of the use of extension primers comprising a 3' portion which is complementary to a portion of a region of double stranded DNA and a 5' oligonucleotide portion which is **not** complementary the region of double standard DNA, but which complementary to a unique known sequence of oligonucleotide tag fixed to a solid substrate. Instead, the extension primers used by Shumaker *et al.* in the gel-based assay are only complementary to a region of their PCR-amplified DNA (see, for example, Fig. 1B, and p. 347, second column). The gel-based assay uses ddNTPs, but Shumaker *et al.* does not suggest the use of these ddNTPs with an extension primer that comprises a 3' oligonucleotide portion that is complementary to a portion of a region of double stranded DNA and a 5' oligonucleotide portion that is not complementary to that region of double stranded DNA.

The second mutation detection method of Shumaker *et al.* is an "Array Primer Extension (APEX) Assay" (see, for example, p. 348). Again, the extension primers of Shumaker *et al.* used in the APEX assay are only complementary to a region of PCR-amplified DNA (see, for example, Fig. 3, and p. 351). Furthermore, this method uses radioactively labeled dNTPs for the primer extension step (see, for example, p. 348, first column, and p. 351, first column), and not distinctly labeled ddNTPs.

Shumaker *et al.* do not teach the use of ddNTPs or radioactively labeled dNTPs with extension primers other than primers that exactly match the target sequence on a region of DNA. Furthermore, Shumaker *et al.* do not suggest the combination of ddNTPs with primers that contain a 3' oligonucleotide portion complementary to a portion of a region of a double stranded DNA, and a 5' oligonucleotide portion which is not complementary to that region of double stranded DNA, but which is complementary to a unique known sequence of an oligonucleotide tag fixed to a solid substrate.

There is no suggestion to combine the teachings of Ugozzoli *et al.*, with the Stratagene Catalog and Shumaker, *et al.* and even if improperly combined, each and every element of the claimed invention is not taught. Thus, a *prima facie* case of obviousness has not been established.

Applicants note that Item 9 recites that Claims 21-24 are rejected under 35 U.S.C. §103(a), but a detailed description of the rejection of independent Claim 22 is not provided.

Claim 23 depends from Claim 22, and Claim 23 has been rejected by the Examiner, stating that "Claim 23 is drawn to an embodiment of Claim 22, wherein solid support is an oligonucleotide array." The Examiner states that Shumaker *et al.* teach this limitation.

Applicants respectfully disagree for the reasons already presented. Shumaker *et al.* in the array method (APEX) for detecting mutations, use radioactively labeled dNTPs, not distinctly labeled ddNTPs. It is apparent that Shumaker *et al.* teaches away from using ddNTPs because they only used ddNTPs in the gel-based assay, which is not an array. For the array method Shumaker *et al.* only use radioactive dNTPs. Thus, there is no teaching or suggestion by Shumaker *et al.* of a kit comprising a set of primers comprising a pair of primers which, when in the presence of a DNA polymerase, amplify a region of double stranded DNA, wherein the region comprises a polymorphic locus, and an extension primer which comprises a 3' portion which is complementary to a portion of the region of double stranded DNA and a 5' oligonucleotide portion which is not complementary to the region of double stranded DNA, but which is complementary to a unique known sequence of a oligonucleotide tag fixed to a solid substrate, wherein the extension primer is complementary to the 3' nucleotide sequence of the polymorphic locus, and wherein the last nucleotide at the 3' end of the extension primer hybridizes exactly one nucleotide before the polymorphic locus; at least two labeled dideoxynucleotides, each of which is distinctly labeled; and a solid support comprising a probe which is attached to a solid support, wherein the probe is complementary to the 5' portion of the extension primer. Furthermore, the references do not suggest a combination of their teachings, and thus a *prima facie* case of obviousness has not been established.

The Examiner has rejected Claim 24 which depends from Claim 22 and recites that the solid support is a bead. The Examiner has stated that Shumaker *et al.* teach this limitation, citing Shumaker *et al.* p. 347-348 under the heading "Gel-based Assay."

Applicants respectfully disagree. As maintained above, Shumaker *et al.* do not teach or suggest all of the claim limitations of Claim 24, as there is no teaching or suggestion of the primers of the present invention. Thus, even the addition of a teaching of a bead fails to establish a *prima facie* case of obviousness when the references, either alone or in combination, fail to teach the claimed invention and when there is no suggestion to combine the teachings of the references.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 25 Under 35 U.S.C. §35 U.S.C. §103(a)

Claim 25 is rejected by the Examiner under 35 U.S.C. §103 (a) as being unpatentable over Ugozzoli *et al.* (GATA 9(4): 107-112 (1992); Ref. U), in view of the Stratagene Catalog (page 39 (1998); Ref. W), and Shumaker *et al.* (Human Mutation 7: 346-354 (1996); Ref. V) as applied above and further in view of Mitsuhashi *et al.* (U.S. Patent 6,251,247 (2001); Ref. A).

The teachings of Ugozzoli *et al.*, the Stratagene Catalog and Shumaker *et al.* are discussed by the Applicants above. Mitsuhashi *et al.* describe an invention using microchannel electrophoresis of RNA. Mitsuhashi *et al.* also describe, in the "Background of the Invention", an assay for determining an amount of total mRNA by capturing mRNA onto oligo (dT)-immobilized microtiter plates (column 1). Oligo (dT) is not an unique sequence; it is complementary to all polyA mRNAs. There is no teaching or suggestion by Mitsuhashi *et al.* to use a microtiter plate as a solid support for a unique known sequence as claimed in the present invention. Thus, without the teaching or suggestion of each and every element of the claimed invention, either alone or in combination, and without a suggestion to combine the teachings of the references, a *prima facie* case of obviousness has not been established.

Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

2. (Three Times Amended) A kit comprising:

(a) an array comprising one or more oligonucleotide tags fixed to a solid substrate, wherein each oligonucleotide tag comprises a unique known arbitrary nucleotide sequence of sufficient length to hybridize to a locus-specific tagged oligonucleotide;

(b) one or more locus-specific tagged oligonucleotides, wherein each locus-specific tagged oligonucleotide has at its first (5') end nucleotide sequence which hybridizes to the arbitrary sequence of a corresponding oligonucleotide tag on the array, and has at it's second (3') end nucleotide sequence complementary to a target polynucleotide sequence in a sample wherein the last nucleotide at the 3' end of the locus-specific tagged oligonucleotide hybridizes exactly one nucleotide before [the] a nucleotide to be queried in the target polynucleotide sequence; and

(c) at least two labeled dideoxynucleotides, each of which is distinctly labeled.